

CLAIMS

1. A method for inhibiting thrombosis in an animal comprising administering an effective dose of an anti-coagulation factor monoclonal antibody having self-limiting neutralizing activity.

2. The method of claim 1 further comprising administering acetylsalicylic acid in combination with the anti-coagulation factor monoclonal antibody.

3. The method of claim 1 or 2 wherein the coagulation factor is from the intrinsic or common coagulation pathway.

4. The method of claim 3 wherein the anti-coagulation factor monoclonal antibody is an anti-Factor IX, anti-Factor IXa, anti-Factor X, anti-Factor Xa, anti-Factor XI, anti-Factor XIa, anti-Factor VIII, anti-Factor VIIIa, anti-Factor V, anti-Factor Va, anti-Factor VII, anti-Factor VIIa or anti-thrombin.

5. The method of claim 3 wherein the anti-coagulation factor monoclonal antibody is an anti-Factor IX.

6. The method of claim 5 wherein the anti-Factor IX monoclonal antibody has the identifying characteristics of SB 249413, SB 249415, SB 249416, SB 2249417, SB 257731 or SB 257732.

7. The method of claim 5 wherein the anti-Factor IX monoclonal antibody has the identifying characteristics of SB 249417.

8. The method of claim 1 or 2 wherein aPTT is prolonged without significant prolongation of PT.

9. The method of claim 4 wherein aPTT is about 35 seconds to about 100 seconds.

10. The method of claim 1 or 2 wherein the thrombosis is associated with myocardial infarction, unstable angina, atrial fibrillation, stroke, renal damage, pulmonary embolism, deep vein thrombosis, percutaneous transluminal coronary angioplasty,

disseminated intravascular coagulation, sepsis, artificial organs, shunts or prostheses.

11. An anti-coagulation factor monoclonal antibody having self-limiting neutralizing activity against the coagulation factor.

12. The monoclonal antibody of claim 11 wherein the coagulation factor is from the intrinsic or common coagulation pathway.

13. The monoclonal antibody of claim 12 wherein the anti-coagulation factor monoclonal antibody is an anti-Factor IX, anti-Factor IXa, anti-Factor X, anti-Factor Xa, anti-Factor XI, anti-Factor XIa, anti-Factor VIII, anti-Factor VIIIA, anti-Factor V, anti-Factor Va, anti-Factor VII, anti-Factor VIIa or thrombin.

14. The monoclonal antibody of claim 12 wherein the anti-coagulation factor monoclonal antibody is an anti-Factor IX.

15. The monoclonal antibody of claim 14 having the identifying characteristics of SB 249413, SB 249415, SB 249416, SB 249417, SB 257731, SB 257732, 9E4(2)F4 or 11G4(1)B9.

16. The monoclonal antibody of claim 14 having the identifying characteristics of SB 249417.

17. A hybridoma having the identifying characteristics of cell line 9E4(2)F4 or 11G4(1)B9.

18. A neutralizing Fab fragment or F(ab')₂ fragment thereof, produced by deleting the Fc region of the monoclonal antibody of claim 11.

19. A neutralizing Fab fragment or F(ab')₂ fragment thereof, produced by chain shuffling whereby the Fd heavy chain of the monoclonal antibody of claim 11 is expressed in a murine light chain filamentous phage Fab display library.

20. A neutralizing Fab fragment or F(ab')₂ fragment thereof, produced by chain shuffling whereby the light chain of the monoclonal antibody of claim 11 is

expressed in a murine heavy chain filamentous phage Fab display library.

21. An immunoglobulin heavy chain complementarity determining region, the amino acid sequence of which is selected from the group consisting of SEQ ID NOs: 8, 9 and 10.

22. A nucleic acid molecule encoding the immunoglobulin complementarity determining region of claim 21.

23. An immunoglobulin light chain complementarity determining region, the amino acid sequence of which is selected from the group consisting of SEQ ID NOs: 12, 13 and 14.

24. A nucleic acid molecule encoding the immunoglobulin complementarity determining region of claim 23.

25. An altered antibody comprising a heavy chain and a light chain, wherein the framework regions of said heavy and light chains are derived from at least one selected antibody and the amino acid sequences of the complementarity determining regions of each said chain are derived from the monoclonal antibody of claim 11.

26. The altered antibody of claim 25 which is humanized.

27. The humanized antibody of claim 26 wherein the heavy chain has the amino acid sequence set forth in SEQ ID NO: 31, 52, or 89.

28. The humanized antibody of claim 26 wherein the light chain has the amino acid sequence set forth in SEQ ID NO: 44, 57, 62, 74, 78 or 99.

29. The humanized antibody of claim 26 wherein the heavy chain has the amino acid sequence set forth in SEQ ID NO: 31 and the light chain has the amino acid sequence set forth in SEQ ID NO: 44.

30. The humanized antibody of claim 26 wherein the heavy chain has the amino acid sequence set forth in SEQ

ID NO: 52 and the light chain has the amino acid sequence set forth in SEQ ID NO: 57.

31. The humanized antibody of claim 26 wherein the heavy chain has the amino acid sequence set forth in SEQ ID NO: 52 and the light chain has the amino acid sequence set forth in SEQ ID NO: 62.

32. The humanized antibody of claim 26 wherein the heavy chain has the amino acid sequence set forth in SEQ ID NO: 52 and the light chain has the amino acid sequence set forth in SEQ ID NO: 74.

33. The humanized antibody of claim 26 wherein the heavy chain has the amino acid sequence set forth in SEQ ID NO: 52 and the light chain has the amino acid sequence set forth in SEQ ID NO: 78.

34. The humanized antibody of claim 26 wherein the heavy chain has the amino acid sequence set forth in SEQ ID NO: 89 and the light chain has the amino acid sequence set forth in SEQ ID NO: 99.

35. A chimeric antibody comprising a heavy chain and a light chain, said antibody characterized by inhibiting the function of intrinsic or common pathway coagulation factors in a self-limiting manner, wherein thrombosis is inhibited and limited modulation of coagulation is produced, wherein the constant regions of said heavy and light chains are derived from at least one selected antibody and the amino acid sequences of the variable regions of each said chain are derived from the monoclonal antibody of claim 11.

36. The antibody according to claim 35 wherein the constant regions are selected from human immunoglobulins.

37. A pharmaceutical composition comprising the altered antibody of claim 26 or 35 and a pharmaceutically acceptable carrier.

38. The pharmaceutical composition of claim 37 further comprising acetylsalicylic acid.